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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NASHED, NASHAAT T	
ART UNIT	PAPER NUMBER
1652	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/914,286	Omura et al.
Examiner	**Art Unit**
Nashaat T. Nashed	1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 30, 2003*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above, claim(s) *8, 9, 15, 17, 22, 23, 29, 30, 34, and 39-42* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-7, 10-14, 16, 18-21, 24-28, 31-33, 35-38, and 43* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Aug 24, 2001* is/are a) ☐ accepted or b) ☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *8 & 10*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Applicant's election with traverse of Group I, claims 1-29, 31-38, and 43, drawn to nucleic acid encoding the polyketide synthase of SEQ ID NO: 3, the polypeptide of SEQ ID NO: 3 and fragment thereof, vector and host cells comprising said nucleic acid, and method of making the polyketide synthase of SEQ ID NO: 3, in Paper No. 12 is acknowledged. The traversal is on the ground(s) that: (1) no lack of unity of invention was found during the international phase of examination; (2) no burden on the examiner to examine the invention of Groups I-IV together; (3) the examiner should examine up to ten independent sequences together (37 CFR 1.141); and the invention of Groups I-IV are related to one another as species. This is not found persuasive for the reasons summarized bellow. The examiner of a national stage application is not bound by the finding in the search report or the written opinion. As indicated in the previous Office action , paper number 9, the polyketide synthases of Groups I-IV are independent chemical entity having different structure and function. Each of the polyketide synthases of Group I-IV is a multifunctional enzyme having different structure, substrate and product. While searches for the four groups may overlap, each polyketide synthase has a different structure which has to be searched independently in the patent and non-patent literature. Thus, searching the four groups together constitute an examination burden. Since some of the claims are directed to specific catalytic modules and catalytic domains can function independently with different catalytic modules and catalytic domains, a restriction based on modules or catalytic domain would have been proper. Because of the interest of the applicant, the restriction was made on the bases of individual open reading frames. With regard to examining up to ten sequences together, the restriction is consistent with the policy of searching up to ten sequences together. First, up to ten sequences together includes searching only a single sequence. The policy is applicable only to nucleic acid sequences, and not applicable in cases where amino acid sequences has to be searched. Finally, the four polyketide synthases of Groups I-IV can not be treated as species. As indicated above, the four polyketide synthases have different structure and function. They have different substrates and products as well as catalytic activities.

The requirement is still deemed proper and is therefore made **FINAL**.

Claim 17 was inadvertently included in Groups I-IV in the previous Office action, paper 9. It is clearly drawn to the subject matter of Group V.

Claims 8, 9, 15, 17, 22, 23, 29, 30, 34, and 39-42 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12.

Claims 1-7, 10-14, 16, 18-21, 24-28, 31-33, 35-38 and 43 are under consideration as they relate only to the open reading frame encoding SEQ ID NO: 3.

New formal drawings are required in this application because some of the letters and the numbers are too small to read. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claims 1-7, 10-14, 16, 18, 20, 21, 26-28, 31-33, 35, 36, 38 and 43 are objected to under 37 CFR § 1.75(d)(1) as being in improper form because the claim states an improper Markush groups. Compounds included within a Markush group must "(1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility." (See MPEP § 803.02.). The various members of the Markush group in the claims are different chemical compound or domains having different structure and function.

Claims 16, 35, 36 and 37 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim can not depend on another multiple dependent claim. See MPEP § 608.01(n). Appropriate corrections are required.

Claim 5-7, 10-14, 20, 21, 24-27, and 33 objected to because of the following informalities:

(a) Claims 5-7, 10-14, 20, 21, and 24-27 contain the phrase "comprising the nucleotide sequence selected from". Said phrase should be "comprising a nucleotide sequence selected from".

(b) Claim 33 contains the phrase "comprising the amino acid sequence selected from". Said phrase should be "comprising an amino acid sequence selected from".

(c) Claim 33, line 12, the word "acida" should be replaced with "acid".

Appropriate correction is required.

35 U.S.C. § 101 reads as follows:
"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 1-7, 10-14, 16, 18-21, 24-28, 31-33 and 43 are rejected under 35 U.S.C. § 101 because the claimed invention is directed toward non-statutory subject matter.

In the absence of the hand of man, naturally occurring proteins and/or nucleic acids are considered non-statutory subject matter. *Diamond v. Chakrabarty*, 206 USPQ 193 (1980). This rejection may be overcome by amending the claims to contain wording such as "An isolated and purified protein or nucleic acid".

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification lacks a sufficient written description for enablement based on deposit requirement.

The invention appears to be directed to a novel microorganism. Since the microorganism is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The claimed microorganism contains a plasmid/vector which its nucleic acid sequence is not fully disclosed, nor have all the sequences required for its construction been shown to be biblically known and freely available. The enablement requirement of 35 U.S.C. § 112 may be satisfied by deposit of the transformed *Streptomyces avermitilis* K2038 (FERM BP-2775). The specification does not disclose a repeatable process to obtain the plasmid/vectors, and it is not apparent if the DNA sequence is readily available to the public. Accordingly, it is deemed that a deposit of the plasmid should have been made in accordance with 37 C.F.R. § 1.801-1.809.

If the deposit was made under the terms of the Budapest Treaty, then an affidavit or declaration by the applicant, or a statement by an attorney of record over his/her signature and registration number, stating that the specific microorganism has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of the patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. § 1.801-1.809, the applicant may provide assurance or compliance by an affidavit or declaration, or by a statement by an attorney of record over his/her signature and registration number, showing that:

(1) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;
(2) all restriction upon availability to the public will be irrevocably removed upon granting of the patent;
(3) the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and
(4) the deposit will be replaced if it should ever become inviable.

Claim 37 is rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 1, 3, 4, 31, 34-36 and 38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 3, 4, 31, 34-36 and 38 are directed to all possible avermectin aglycon synthase, i. e., presumably, any polyketide synthase involved in the biosynthesis of avermectin aglycon, and genes encoding them from any biological source. The specification, however, only provides a single representative species from *S. avermitilis* having the nucleic acid sequence corresponds to residues 1-11916 of SEQ ID NO: 1 and encodes the amino acid sequence of SEQ ID NO: 3. Applicants should note that the polyketide synthase of SEQ ID NO: 3 has different structure and function from the other polyketide synthases taught in the specification and isolated from the same biological source. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional representative species of these DNAs and polypeptide by any identifying structural characteristics or properties other than the multienzymatic activities and the amino acid sequence, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention. The insertion of a structural feature in the claims such as nucleic acid or amino acid sequence would overcome this rejection.

Claims 1, 3, 4, 16, 31-33, 35, 36, 38, and 43 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the nucleic acid encoding the polyketide synthase of SEQ ID NO: 3 and the various catalytic modules and domain comprised in SEQ ID NO: 3. The specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims. The

claims are broader than the enablement provided by the disclosure with regard to the huge number of all possible polyketide synthases, modules and domains capable of carrying out a chemical transformation which may produce avermectin, and those polypeptides having one or more amino acid residues deleted, replaced or added to the amino acid sequence of SEQ ID NO: 3 and its catalytic domains. Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses any polypeptide or oligonucleotide encoding said polypeptide which can carry out a chemical transformation leading to avermectin or precursor thereof. The specification provides guidance and examples in the form of an assay to isolate the DNA encoding the gene cluster require for the biosynthesis of avermectin aglicon, characterize the various open reading frame and the catalytic modules and their domains from *S. avermitilis*, and introducing a disabling mutation in the dehydratase domain in module 2 of SEQ ID NO: 3, see examples 1 and 2. While molecular biological techniques and genetic manipulation to clone genes and characterize the cloned gene, or make any insertion, deletion, substitution, and combination thereof mutant are known in the prior art and the skill of the artisan are well developed, knowledge of biological source of gene cluster that encodes a protein or a polypeptide able to carry out at least one chemical transformation leading to avermectin, the amino acids to be deleted, substituted, and/or inserted in SEQ ID NO: 3, or the mutant polypeptide or nucleic acid encoding said polypetide that contains one or more catalytic domain having enhanced catalytic activity(ies) is lacking. Thus, searching for a gene cluster which contains a polyketide synthase or catalytic module or domain capable of carrying out a chemical transformation to produce avermectin or precursor thereof or mutants of SEQ ID NO: 3 having at least one or more residue deleted, substituted, inserted or combination thereof is well outside the realm of routine experimentation and predictability in the art of success is extremely low. The amount of experimentation to clone a gene cluster encoding for the biosynthesis of avermectin or precursor thereof is enormous. Since routine experimentation in the art does not include screening gene libraries constructed from any biological or man made source where the expectation of obtaining the desired nucleic acid or polypeptide is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the biological source of the gene cluster, the nucleic acid sequence homology between the nucleic acid sequence having the nucleic acid sequence corresponding to residues 1-11916 of SEQ ID NO: 3 and other nucleic acid sequences encoding functionally identical polypeptide, the homology between SEQ ID NO: 3 and other functionally identical

polyketide synthase, and the amino acid residues to be deleted, inserted or substituted with predictable effects on the catalytic activity. Without such a guidance, the experimentation left to those skilled in the art is undue. It should be pointed out that substituting one module by another with different catalytic activity or substituting one catalytic domain by another with different specificity is known in the prior art. Therefore, claims directed to such a mutant would be enabled in the instant application provided that they have support in the specification.

Claims 1-7, 10-14, 16, 18-21, 24-28, 31-33, 35-38 and 43 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections:

(a) The phrases "avermectin aglycon synthase" in claim 1, "avermectin aglycon synthase activity" in claim 2, "avermectin aglycon synthase domains" in claims 3 and 4, "avermectin aglycon synthase domain" in claim 18 render the claims indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. The phrase "avermectin aglycon synthase" is not defined in the specification. One of ordinary skill in the art would interpret the phrase as the last enzyme which is required for the biosynthesis avermectin, i. e., the thioesterase activity or the polypeptide containing the thioesterase activity. The elected subject matter in the instant application is directed to the polypeptide of SEQ ID NO: 3 and the nucleic acid encoding said polypeptide. While the polypeptide of SEQ ID NO: 3 can be named a polyketide synthase, it can not be named "avermectin aglycon synthase" because the product of its catalytic activity is a triketide and not avermectin, see Figure 2. For examination purposes, the following is assumed: (a) "avermectin aglycon synthase" : the polyketide synthase of SEQ ID NO: 3, a functionally identical polyketide synthase or a fragment thereof having any of the activities found in SEQ ID NO: 3; (b) "avermectin aglycon synthase activity": an activity selected from AT' and ACP' (known in the prior art as the loading domain), KS1, AT1, KR1, ACP1, KS2, AT2, DH2, KR2 , and ACP2; and (c) "avermectin aglycon synthase domains" and"avermectin aglycon synthase domain": a protein domain having a catalytic activity selected from AT', ACP', KS1, AT1, KR1, ACP1, KS2, AT2, DH2, KR2 , and ACP2.

(b) The unspecified catalytic or functional activities listed in claim 4 render the claims indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. For examination purposes, the catalytic activities are assumed to be AT', ACP', KS1, AT1, KR1, ACP1, KS2, AT2, DH2, KR2 , and ACP2.

(c) The phrase "under stringent condition" in claims 5-7, 10-14, 18-21, and 24-28 renders the claims indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. There are several sets of hybridization conditions known in the prior art as "stringent hybridization conditions". The result of a hybridization experiment would vary with the set of stringent hybridization conditions used. Since the specification has not identified any hybridization conditions and one of ordinary skill in the art would not know which one of the known hybridization conditions applicants are referring to, the claims are found indefinite.

(d) The activities named in claims 5-7, 10-14, 18-21, 24-27 and 33 render the claims indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. For examination purposes only, they are assigned appropriately to one of the activities found in the polyketide of SEQ ID NO: 3: AT', ACP', KS1, AT1, KR1, ACP1, KS2, AT2, DH2, KR2 , and ACP2.

(e) The phrase " a polypeptide comprising an amino acid sequence wherein one or more amino acids are deleted, replaced or added in the amino acid sequence of SEQ ID NO: 3" in claims 32 and 33 renders the claims indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired.. Since all polypeptides are related to one another by deletion, substitution and/or addition, the claim interpreted as any polypeptide having any sequence homology to SEQ ID NO: 3.

(f) claims 16, 31, 34-38 and 43 are included in these rejection because they are dependent on rejected claims and do not cure its deficiencies.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 4, 34-36 and 43 are rejected under 35 U.S.C. § 102(b) as being anticipated by Gewain *et al.* [U. S. Patent 5,262,474 (474)].

The 474 patent teach the cloning of the gene cluster from *Streptomyces avermilitis* (claim 1), see at least the abstract and Figure 3. While the 474 patent has not identified the various domains and all the specific catalytic activities of the gene cluster, the catalytic domains and their catalytic activities are intrinsic properties of the proteins encoded by the gene cluster taught in the 474 patent (claims 3 and 4). Also, it teaches recombinant

vectors and host cell including avermectin producing bacterial strains comprising the gene clusters or fragments there of (34-36), see examples 2-5. The 110 kb gene cluster taught in the 474 patent has 5 to 60 contagious nucleotide from a nucleic acid encoding avermectin aglycon synthase.

Claims 1, 3, 4, 31, 34, 35 and 43 are rejected under 35 U.S.C. § 102(b) as being anticipated by Marsden *et al.* [IDS: Science 1998, 279, pages 199-202].

Marsden *et al.* teach the construction of two hybrid polyketide synthase consisting of the AT' and ACP' domains (loading domain) from *Streptomyces avermilitis* fused to modules 1 and 2, and 1 and 2 as well as the thioesterase domain from the DEBS gene cluster, see figures 1A and 1B. They constructed a nucleic acid sequence encoding said hybrid polyketide synthase, a vector comprising said nucleic acid, transformed the vector to a host cell, and expressed the protein in a host cell (claim 1, 3, 4, 34, and 35), see page 201, right column item 19. The two hybrid polyketide synthases are shown to be functional and produce novel polyketides. The nucleic acid molecules taught by Marseden *et al.* have 5 to 60 contagious nucleotide of the nucleic acid of claim 1 (claim 43).

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 2-7, 10-14, 18-21, 24-28, and 34-37 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Gewain *et al.* [U. S. Patent 5,262,474 (474)].

The teaching of the 474 patent is summarized above. Claims 2-7, 10-14, 18-21, 24-28, and 34-37 are directed to: (a) specific nucleic acid sequences comprising the entire open reading frame encoding the amino acid sequence of SEQ ID NO: 3 or catalytic fragments thereof; and (b) nucleic acid molecule which hybridizes under any stringent conditions to the nucleic acid of (a). Although the 474 patent does not teach any nucleic acid sequences, the claimed nucleic acid sequences are inherent properties of the gene cluster taught in the 474 patent.

The nucleic acid molecule taught in the 474 patent appears to be identical to that of the instant application. The gene cluster taught in the 474 is from the same biological source as that used by the applicants, i. e., *Streptomyces avermilitis* of the instant application. The gene cluster of the instant application and that taught in the 474 patent encode the biosynthetic pathway for the same natural products. Other evidence are found in MacNeil, D. J. [Biotechnology 28, 421-442 (1995)]. Figure 19-9 of MacNeil shows the organization of the gene cluster taught in the 474 patent with the various modules and catalytic domains and activities which include the loading domain, i. e., (AT' + ACP'), and modules 1 and 2 corresponding to the polyketide of SEQ ID NO: 3. Also, it is similar to part one of Figure 3 of the instant application.

These rejections are being made under 35 U.S.C. § 102(b) and 35 U.S.C. § 103 because it is not possible for the Examiner to physically compare the claimed nucleic acid sequences encoding the polyketide synthase of SEQ ID NO: 3 and fragments thereof; or those that hybridized to said nucleic acid under any hybridization conditions to those taught in the 474 patent. Applicant bears the burden of providing evidence which distinguishes the claimed nucleic acid sequences of the instant application and those disclosed in the 474 patent. A preferred means of providing this evidence is for applicant to submit a side-by-side comparison between the claimed nucleic acid sequences of the instant application and that of the 747 patent which demonstrates any material differences and shows the claimed nucleic acid encoding the polyketide synthase of SEQ ID NO: 3 to be distinct and unobvious in view of the enzymes of the prior art. *In re Best, Bolton, and Shaw* 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald, Sanders and Bagheri* 205 USPQ 594 (CCPA 1980).

Claims 2-5, 10, 11, 18, 19, 24, 25, 31, 34 and 35 are rejected under 35 U.S.C. § 102(b) as being anticipated by Marsden *et al.* [IDS: Science 1998, 279, pages 199-202].

The teaching of the Marsden *et al.* is summarized above. Claims 2-5, 10, 11, 18, 19, 24, 25, 31, 34 and 35 are directed to: (a) specific nucleic acid sequences comprising the entire open reading frame encoding the amino acid sequence of SEQ ID NO: 3 or catalytic fragments thereof, in particular the AT' and ACP' domains; and (b) nucleic acid molecule which hybridizes under any stringent conditions to the nucleic acid of (a). Although the Marsden *et al.* do not teach any nucleic acid sequences, the nucleic acid sequences and the polyketide synthase claimed are inherent properties of the nucleic acid and hybrid polypeptide taught by Marsden *et al.*.

The nucleic acid molecule and the hybrid polypeptide taught by Marsden *et al.* appears to be identical to those claimed in the instant application. The nucleic acid encoding the starter domain (AT'ACP') as well as the polypeptide comprising said domain taught by Marsden *et al.* is from the same biological source as that used by the applicants, i. e., *Streptomyces avermilitis* of the instant application and prepared from the gene cluster reported in the 474 patent. As indicated above, the gene cluster of the instant application and that taught in the 474 patent encode the biosynthetic pathway for the same natural products. Other evidence are found MacNeil, D. J. [Biotechnology 28, 421-442 (1995)]. Figure 19-9 shows the organization of the gene cluster taught in the 474 patent with the various modules and catalytic domains and activities which include module 1 and 2 corresponding to the polyketide of SEQ ID NO: 3. Also, it is similar to part one of Figure 3 of the instant application.

These rejections are being made under 35 U.S.C. § 102(b) and 35 U.S.C. § 103 because it is not possible for the Examiner to physically compare the claimed nucleic acid sequences encoding the starter domain of polyketide synthase of SEQ ID NO: 3 and that taught by Marsden *et al.* Applicant bears the burden of providing evidence which distinguishes the claimed nucleic acid sequences of the instant application and those disclosed in Marsden *et al.* A preferred means of providing this evidence is for applicant to submit a side-by-side comparison between the claimed nucleic acid sequence and the polypeptide of the instant application and those taught by Marsden *et al.* which demonstrates any material differences and shows the claimed nucleic acid encoding the starter domain of the polyketide synthase of SEQ ID NO: 3 to be distinct and unobvious in view of the enzymes of the prior art. *In re Best, Bolton, and Shaw* 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald, Sanders and Bagheri* 205 USPQ 594 (CCPA 1980).

Claims 16, 31-33, and 38 are rejected under 35 U.S.C. § 103 as being unpatentable over Gewain *et al.* [U. S. Patent 5,262,474 (474)] in view of MacNeil, D. J. [Biotechnology 28, 421-442 (1995)] and Marsden *et al.* [IDS: Science 1998, 279, pages 199-202].

The teachings of the 474 patent are summarized above, but the 474 patent does not teach the polypeptides taught by the gene cluster *Streptomyces avermilitis*.

MacNeil teaches the organization of the gene cluster taught in the 474 patent with the various modules and catalytic domains and activities which include module 1 and 2 corresponding to the polyketide of SEQ ID NO: 3, see MacNeil.Figure 19-9.

The teachings of Marsden *et al.* are summarized above.

The 474 patent provide one of ordinary skill in the art with a motivation to make the polyketide synthases of *Streptomyces avermilitis* as it teaches compounds having potent anthelmintic and insecticidal activities produced by said bacterium, see column 2, lines 10-13. Thus, it would have been obvious to one of ordinary skill in the art at the time of invention to obtain the gene cluster, construct an expression vector, transform a host cell such as *S. avermilitis* as taught in the 474 patent, culture the cell under condition suitable for the expression of the gene cluster, and purify the polyketide synthases produced (claim 31-33 and 38) to use *in vitro* method to make the anthelmintic and insecticidal compounds. Alternatively, the ordinary skill in the art would have sequenced the gene cluster and identify the various open reading frames which include the polypeptide consisting of the starter domain and modules 1 and 2. The ordinary skill in the art would be further motivated to produce each of the polypeptides encoded by the gene cluster separately for easy purification. The separately prepared polyketide synthases may be used either in making the avermitis compounds or precursor thereof. Also, the ordinary skilled artisan would have been further motivated and able to identify the various catalytic domains in the gene cluster described by MacNeil and uses the nucleic acid encoding the various catalytic domain to make hybrid polyketide synthases as taught by Marsden *et al.* or disable a catalytic domain by mutation using well known methods in the art (claim 16) to generate novel avermitis compounds. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is (703) 305-6586. The examiner can normally be reached Monday, Tuesday, Thursday, and Friday from 9:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (703) 308-3804. The fax phone numbers for this Group are (703) 305-3014 and (703)308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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Primary Examiner